

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 799

[OPTS-42061B; FRL 3130-8(b)]

Oleilamine; Proposed Test Standards

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed Rule.

SUMMARY: This document proposes that the Toxic Substances Control Act (TSCA) test guidelines be used as the test standards by manufacturers and processors to test oleilamine (9-octadecenylamine or ODA, CAS Number 112-90-3) for developmental toxicity, and to conduct two-tiered mutagenicity testing of ODA which may indicate the need for third-tier mutagenicity and oncogenicity testing following public program review. This notice also proposes deadlines for the submission of such test data. Elsewhere in this issue of the *Federal Register*, a final rule to require ODA testing in accordance with section 4(a) of TSCA is also published.

DATES: Submit written comments on or before October 8, 1987. If persons request time for oral comment by September 23, 1987, EPA will hold a public meeting on this proposed rule in Washington, DC. For further information on arranging to speak at the meeting, see Unit VI. of this preamble.

ADDRESS: Submit written comments, identified by the document control number (OPTS-42061B) in triplicate to: TSCA Public Information Office (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm. NE-G004, 401 M St., SW, Washington, DC 20460.

A public version of the administrative record supporting this action (with any confidential business information deleted) is available for inspection at the above address from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

FOR FURTHER INFORMATION CONTACT: Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Rm. E-543, 401 M St., SW., Washington, DC 20460, (202-554-1404).

SUPPLEMENTARY INFORMATION: Elsewhere in this issue of the *Federal Register*, EPA is issuing a final test rule under section 4(a) of TSCA to require certain toxicity testing of ODA. The Agency is now proposing test standards to be used and deadlines for submission of the required test data.

I. Background

Elsewhere in this issue of the *Federal Register*, EPA is issuing a Phase I final rule pursuant to TSCA section 4 that establishes testing requirements for manufacturers and processors of ODA. This Phase I rule specifies the following testing requirements for ODA: Oral developmental toxicity, and a two-tiered mutagenicity scheme which may indicate the need for third-tier mutagenicity and oncogenicity testing following public program review.

Once this Phase I test rule becomes effective, manufacturers and processors of ODA would normally be required (under the two-phase process) to submit proposed study plans for each of the studies required, and proposed schedules for both the initiation of testing and the submission of study data (see 40 CFR 790.50). EPA would review the submitted study plans and schedules and would subsequently issue them (with any necessary modifications) in a Phase II test rule proposal. This proposal would request public comment on the suitability of the proposed study plans for purposes of ensuring that the resulting data would be reliable and adequate. After evaluating and responding to public comment, EPA would adopt the study plans, including the reporting schedules, in a Phase II final rule as the required test standards and data submission deadlines (see 40 CFR 790.52).

However, in the case of the ODA test rule, which was initiated under the two-phase process, EPA has decided to propose relevant TSCA test guidelines as the test standards (see Unit III. below). In addition, EPA is proposing that the data from the required studies be submitted within certain time periods. These time periods will serve as the data submission deadlines required by TSCA section 4(b)(1) (see Unit IV. below). The reasons for this deviation from the standard test rule process are discussed below.

II. Change in the Test Rule Development Process

A. Test Standards and Data Submission Deadlines

TSCA section 4(b)(1) specifies that test rules shall include standards for the development of test data ("test standards") and deadlines for submission of test data. Under a two-phase process utilized by EPA since 1982 (47 FR 13012; March 26, 1982) and formally adopted in the fall of 1984 (49 FR 39744; Oct. 10, 1984), test standards and data submission deadlines were to be adopted during the second phase of the rulemaking process. Upon issuance

of the Phase I final rule, which established the effects and characteristics for which a given chemical substance must be tested, persons subject to the rule would be required by a specified date to submit study plans detailing the methodologies and protocols they intended to use to perform the required tests. Such study plans were to include proposed schedules for the initiation and completion of testing and submission of test data (see 40 CFR 790.50(a) and (c)). In the second phase, after consideration of public comment, the Agency would promulgate the Phase II final rule adopting the study plans (with any necessary modifications) as the test standards for the development of test data and deadlines for submission of test data.

In December 1983, the Natural Resources Defense Council and the Industrial Union Department of the American Federation of Labor-Congress of Industrial Organizations filed an action under TSCA section 20 which challenged, among other things, the use of the two-phase process. In an August 23, 1984 Opinion and Order, the Court found that utilization of the two-phase rulemaking process was permissible. However, the Court also held that the Agency was subject to a standard of promulgating test rules within a reasonable time. *NRC v. EPA*, 595 F. Supp. 1255 (S.D.N.Y. 1984).

After that Opinion, the Agency decided to expedite test rules by using a single-phase rulemaking process for most test rules. In the document announcing this decision (50 FR 20652, 20653; May 17, 1985), EPA stated that the single-phase approach offers a number of advantages over the two-phase process. In the single-phase approach, the Agency proposes (in one document) not only the effects for which testing will be required but also proposes pertinent TSCA or other appropriate guidelines as the test standards and deadlines for the submission of test data. After receiving and evaluating public comment on the proposed testing requirements, test guidelines, and data submission deadlines, EPA promulgates a final test rule.

This single-phase approach shortens the rulemaking period and expedites the initiation of required testing that would usually result from use of the two-phase rulemaking process. The single-phase process also eliminates the requirements under the two-phase approach for industry to submit test protocols for approval. Moreover, by allowing the submission of alternative testing methodologies, the single-phase

approach preserves the flexibility of the two-phase process.

These same advantages, i.e., expediting testing and eliminating study plan submission requirements for persons subject to a Phase I rule, are factors considered by EPA in deciding to modify the rulemaking process for ODA. By proposing both pertinent TSCA test guidelines as the test standards and data submission deadlines at the time of issuance of the Phase I final rule, EPA expects that the Phase II final rule will be issued 6 months sooner than would occur if the usual two-phase process were followed. Thus, required testing will be initiated sooner. In addition, for the required tests for ODA, appropriate TSCA test guidelines are available (see Unit III. below).

B. Modifications to Requirements Under a Phase I Final Rule for ODA

Persons subject to the ODA Phase I final rule who have notified EPA of their intent to test would normally be required to submit study plans and proposed data submission deadlines within a specified time from the final rule's effective date (see 40 CFR 790.50(a) and (c)). Because EPA is proposing certain TSCA guidelines as the test standards and data submission deadlines, persons subject to the Phase I final rule are not required to submit study plans for the required testing or to propose dates for the initiation and completion of that testing. Manufacturers and processors of ODA are invited to comment on the proposed data submission deadlines. The Agency will consider these comments in issuing the Phase II final rule.

Persons subject to the Phase I final rule for ODA are still required to submit notices of intent to test or exemption applications in accordance with 40 CFR 790.55. Moreover, once the test standard is promulgated in the Phase II final rule, those persons who have notified EPA of their intent to test must submit study plans (which adhere to the promulgated test standards) no later than 45 days before the initiation of each required test (see 40 CFR 790.50(a)(1)).

III. Proposed Test Standards

The Phase I rule specifies the following testing requirements for ODA: Developmental toxicity, and a two-tiered mutagenicity scheme which may indicate the need for third-tier mutagenicity and oncogenicity testing following public program review.

The mutagenicity testing includes tests for both chromosomal aberration and gene mutation. The *in vitro* cytogenetics and Ames assays of the first tier will not be required because

they have been completed by the Oleylamine Program Panel of the Chemical Manufacturers Association and have been found negative.

The testing required in the phase one rule for ODA is in stages. First-stage tests consist of developmental toxicity and the remaining first-tier mutagenicity tests: *in vivo* mammalian bone marrow cytogenetics test and a detection of gene mutation in somatic cells in culture. If the results of either of the first-tier mutagenicity tests are positive, the second tier of mutagenicity tests, consisting of a rodent dominant lethal assay and/or a sex linked recessive lethal test in *Drosophila melanogaster*, must be conducted. The Agency will review these data as received together with other relevant data and hold a public meeting before requiring initiation of the second-stage testing, which includes third-tier mutagenicity, consisting of the rodent heritable translocation assays and/or the mouse visible specific locus test, plus oncogenicity. Test sponsors will be notified by Federal Register notice or certified letter of second-stage testing decisions.

The Agency is now proposing that testing of ODA for developmental toxicity, mutagenicity, and oncogenicity be conducted using as test standards the TSCA test guidelines specified under 40 CFR Parts 796, 797, 798 and modified as specified in the Federal Register of May 20, 1987 (52 FR 19056). The specific test standards being proposed are as follows:

1. *Specific Organ/Tissue Toxicity:* Developmental Toxicity Study which appears at 40 CFR 798.4900.

2. *Genetic Toxicity:* Chromosomal Effects.

i. First Tier: *In Vivo* Mammalian Bone Marrow Cytogenetics Test: Chromosomal Analysis which appears at 40 CFR 798.5385.

ii. Second Tier: Rodent Dominant Lethal Assay which appears at 40 CFR 798.5450.

iii. Third Tier: Rodent Heritable Translocation Assay which appears at 40 CFR 798.5460.

3. *Genetic Toxicity:* Gene Mutations.

i. First Tier: Detection of Gene Mutation in Somatic Cells in Culture which appears at 50 CFR 798.5300.

ii. Second Tier: Sex-Linked Recessive Lethal Test in *Drosophila melanogaster* which appears at 40 CFR 798.5275.

iii. Third Tier: Mouse Visible Specific Locus Test which appears at 40 CFR 798.5200.

4. *Chronic Exposure:* Oncogenicity which appears at 40 CFR 798.3300.

EPA believes that the TSCA Health Effects Test Guidelines cited above, if

properly followed, should produce adequate and reliable data.

Certain modifications to the test guidelines which the Agency feels are necessary for testing of ODA are summarized below:

1. *Developmental toxicity study.* Two test species are required by EPA, since it is well documented that multiple-species testing is more effective in detecting developmental toxicants than is single-species testing. Although the expected route of human contact is dermal, EPA is requiring the oral route of administration for developmental toxicity testing of ODA. The data base of background information on developmental toxicity studies conducted via the dermal route is very limited, while the data base for the oral route is much more extensive. Moreover, dermal application of the corrosive ODA could stress the test animals, which may itself produce developmental toxicity. Most importantly, a developmental toxicity study is designed to ensure that the agent being tested is administered at a sufficient dose to penetrate to the target system. One thus determines if the agent, under the conditions of exposure with consideration of maternal effects, has the potential to produce an adverse effect. A dermal study may not allow this determination, especially when skin corrosion occurs.

2. i. *In vivo mammalian bone marrow cytogenetics test.* Mice are selected as the species of choice to allow species consistency among the tests in this sequence. The oral route shall be used to maintain consistency among the tests for ODA, and to avoid corrosiveness associated with dermal application.

ii. *Rodent dominant lethal assay.* Mice are selected as the species of choice to maintain species consistency among the tests in this sequence. The oral route shall be used to maintain consistency among the tests for ODA and to avoid corrosiveness associated with dermal application.

iii. *Rodent heritable translocation assays.* Mice are selected as the species of choice to maintain consistency among the tests in this sequence. The oral route shall be used to maintain consistency among the tests for ODA and to avoid corrosiveness associated with dermal application.

3. i. *Detection of gene mutation in somatic cells in culture.* The gene mutation in somatic cells in culture assay (CHO/HGPRT) has already been done and the results are equivocal. Under the assumption that a repeat of the gene mutation assay in the same cell line would result in similar toxicity problems, it is now proposed that the

assay be conducted in a different cell line, mouse lymphoma L5178Y. Aroclor 1254-induced rat liver S-9 is the chosen source of metabolic activation because of its historical data base and generally accepted use in this assay. Alternative dosing procedures shall be used which consist of the use of suspension cultures or roller-bottle incubation.

ii. *Sex-linked recessive lethal test in Drosophila melanogaster*. The oral route of administration shall be used to maintain consistency among the tests for ODA.

iii. *The mouse visible specific locus test*. Mice are selected as the species of choice to allow species consistency between the tests in this sequence; strains (C₃H×101)F₁ or (101×C₃H)F₁ hybrids are chosen because of the historical data base available for these strains. Two dose levels shall be used because dose-responses are essential for risk determination. The oral route of administration shall be used to maintain consistency among the tests for ODA and to avoid corrosiveness associated with dermal application.

4. *Oncogenicity bioassay*. Rats and mice are the species of choice because of their relatively short life spans, the limited cost of their maintenance, their widespread use in pharmacological and toxicological studies, their susceptibility to tumor induction, and the availability of inbred or sufficiently characterized strains. Although the expected route of human contact is dermal, the oral route of administration is required, because the long-term administration of ODA via the dermal route is too stressful for the test species because of the chemical's corrosiveness.

IV. Reporting Requirements

EPA is proposing that all data developed under this rule be reported in accordance with its TSCA Good Laboratory Practice (GLP) standards which appear at 40 CFR Part 792.

Test sponsors are required to submit individual study plans at least 45 days prior to the initiation of each study.

EPA is required by section 4(b)(1)(c) of TSCA to specify the time period during which persons subject to a test rule must submit test data. Studies shall be conducted and interim progress reports shall be provided at 6-month intervals beginning 6 months after the effective date of the final test rule or notification that testing should be initiated. The Agency is proposing specific reporting requirements for each of the proposed test standards as follows:

The developmental toxicity study shall be conducted and the final results submitted to the Agency within 12

months of the effective date of the final test rule.

The mutagenicity studies shall be conducted, and the final results submitted to the Agency as follows:

1. *In vivo* mammalian bone marrow cytogenetics test and detection of gene mutations in somatic cells in culture within 8 months of the effective date of the final rule.

2. Rodent dominant lethal assay and sex linked recessive lethal test in *Drosophila melanogaster* within 17 months of the effective date of the final rule.

3. Rodent heritable translocation assays within 24 months and mouse visible specific locus test within 48 months of EPA's notification of the test sponsor by certified letter or Federal Register notice that testing should be initiated.

Oncogenicity testing shall be conducted and the final results submitted within 53 months of EPA's notification of the test sponsor by certified letter or Federal Register notice that testing should be initiated.

As required by TSCA section 4(d), the Agency plans to publish in the Federal Register a notice of the receipt of any test data submitted under this test rule within 15 days of receipt of that data. Except as otherwise provided in TSCA section 14, such data will be made available for examination by any person.

V. Issues for Comment

EPA invites comment on the use of the proposed TSCA test guidelines as the test standards for the required testing of ODA. EPA also invites comment on the proposed schedules for the required testing.

VI. Public Meetings

If persons indicate to EPA that they wish to present oral comments on this proposed rule to EPA officials who are directly responsible for developing the rule and supporting analyses, EPA will hold a public meeting subsequent to the close of the public comment period in Washington, DC. Persons who wish to attend or to present comments at the meeting should call the TSCA Assistance Office (TAO): (202-554-1404), by September 23, 1987. A meeting will not be held if members of the public do not indicate that they wish to make oral presentations. While the meeting will be open to the public, active participation will be limited to those persons who arranged to present comments and to designated EPA participants. Attendees should call the TAO before making travel plans to verify whether a meeting will be held.

Should a meeting be held, the Agency will transcribe the meeting and include the written transcript in the public record. Participants are invited, but not required, to submit copies of their statements prior to or on the day of the meeting. All such written materials will become part of EPA's record for this rulemaking.

VII. Public Record

EPA has established a record for this rulemaking [docket number (OPTS-42061B)]. This record includes basic information considered by the Agency in developing this proposal, and appropriate Federal Register notices. The Agency will supplement the record with additional information as it is received.

This record includes the following information:

(1) Federal Register notices pertaining to this proposed test standard consisting of: Final Phase I rule on ODA.

(2) TSCA Health Effects Test Guidelines for Developmental Toxicity, Genetic Toxicity, and Oncogenicity.

Confidential Business Information (CBI), while part of the record, is not available for public review. A public version of the record, from which CBI has been deleted, is available for inspection from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays, in Rm. NE-G004 401 M St., SW., Washington, DC 20460.

VIII. Other Regulatory Requirements

A. Executive Order 12291

Under Executive Order 12291, EPA must judge whether a regulation is "major" and therefore subject to the requirements of a Regulatory Impact Analysis. This test rule is not major because it does not meet any of the criteria set forth in section 1(b) of the Order. The economic analysis of the testing of ODA is discussed in the Phase I test rule which appears elsewhere in this issue of the Federal Register.

B. Regulatory Flexibility Act

Under the Regulatory Flexibility Act, (15 U.S.C. 601 *et seq.*, Pub. L. 96-354, September 19, 1980), EPA is certifying that this test rule, if promulgated, will not have a significant impact on a substantial number of small businesses for the following reasons:

1. There are no small businesses known to EPA that are manufacturing ODA.

2. Small processors will not perform testing themselves, or participate in the organization of the testing effort.

3. Small processors will experience only very minor costs, if any, in securing exemption from testing requirements.

4. Small processors are unlikely to be affected by reimbursement requirements, and any testing costs passed on to small processors through price increases will be small.

C. Paperwork Reduction Act

The Office of Management and Budget (OMB) has approved the information collection requirements contained in the proposed rule under the provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 *et seq.*, and has assigned OMB control number 2070-0033. Comments on these requirements should be submitted to the Office of Information and Regulatory Affairs: OMB; 726 Jackson Place NW.; Washington, DC 20503, marked "Attention: Desk Officer for EPA." The final rule package will respond to any OMB or public comments on the information collection requirements.

List of Subjects in 40 CFR Part 799

Testing, Environmental protection, Hazardous substances, Chemicals, Recordkeeping and reporting requirements.

Dated: August 7, 1987.

J.A. Moore,

Assistant Administrator for Pesticides and Toxic Substances.

Therefore, it is proposed that Part 799 be amended as follows:

PART 799—[AMENDED]

a. The authority citation for Part 799 continues to read as follows:

Authority: 15 U.S.C. 2603, 2611, 2625.

b. By amending § 799.3175 by adding new paragraphs (c)(1) (ii) and (iii); (2) (ii) and (iii); (3) (ii) and (iii); and (4) (ii) and (iii) to read as follows:

§ 799.3175 Oleylamine.

• • • • •

(c) • • • • •

(1) • • • • •

(ii) *Test standard.* (A) The developmental toxicity study shall be conducted with ODA in accordance with § 798.4900 of this chapter except the provisions of paragraphs (e)(1)(i) and (5).

(B) For purposes of this section, the following provisions also apply.

(1) *Animal selection.* The rat and rabbit are the required test species.

(2) *Exposure route.* The route of exposure shall be oral.

(iii) *Reporting requirements.* (A) The developmental toxicity testing shall be completed and the final results

submitted to the Agency within 12 months of the effective date of the final test rule.

(B) Interim progress reports shall be provided at 6-month intervals beginning 6 months after the effective date of the final test rule.

(2) • • • • •

(ii) *Test standard.* (A)(1) The *in vivo* mammalian bone marrow cytogenetics tests: Chromosomal analysis shall be conducted with ODA in accordance with § 798.5385 of this chapter except the provisions of paragraphs (d)(3)(i) and (5)(iii).

(2) For purposes of this section, the following provisions also apply.

(i) *Animal selection.* The mouse is the required test species.

(ii) *Exposure route.* The route of exposure shall be oral.

(B)(1) The rodent dominant lethal assay shall be conducted with ODA in accordance with § 798.5450 of this chapter except the provisions of paragraphs (d)(3)(i) and (5)(iii) if a positive result occurs in the *in vivo* mammalian bone marrow cytogenetics tests: Chromosomal analysis conducted pursuant to paragraph (c)(2)(ii)(A) (1) and (2) of this section.

(2) For purposes of this section, the following provisions also apply.

(i) *Animal selection.* The mouse is the required test species.

(ii) *Exposure route.* The route of exposure shall be oral.

(C)(1) The rodent heritable translocation assays shall be conducted with ODA in accordance with § 798.5460 of this chapter except the provisions of paragraphs (d)(3)(i) and (5)(iii) if a positive result occurs in the rodent dominant lethal assay conducted pursuant to paragraph (c)(2)(ii)(B) of this section if required following a public program review.

(2) For purposes of this section, the following provisions also apply.

(i) *Animal selection.* The mouse is the required test species.

(ii) *Exposure route.* The route of exposure shall be oral.

(iii) *Reporting requirements.* (A) The chromosomal aberration tests shall be completed and the final results submitted to the Agency as follows:

(1) The *in vivo* mammalian bone marrow cytogenetics test within 8 months of the effective date of the final test rule.

(2) The rodent dominant lethal assay (if required) within 17 months of the effective date of the final test rule.

(3) The rodent heritable translocation assays (if required) within 24 months of EPA's notification of the test sponsor by certified letter or Federal Register notice that testing should be initiated.

(B) Interim progress reports shall be provided at 6-month intervals beginning 6 months after the effective date of the final test rule or notification that testing should be initiated.

(3) • • • • •

(ii) *Test Standard.* (A)(1). The detection of gene mutations in somatic cells in culture shall be conducted with ODA in accordance with § 798.5300 of this chapter except the provisions of paragraphs (d)(3)(i) and (4).

(2) For purposes of this section, the following provisions also apply.

(i) *Cells.* ODA shall be tested in L5178Y mouse lymphoma cells.

(ii) *Metabolic activation.* The metabolic activation system shall be derived from the postmitochondrial fraction (S-9) of livers from rats pretreated with Aroclor 1254.

(iii) *Dosing procedures.* Alternative dosing procedures consisting of suspension cultures or roller-bottle incubation shall be used.

(B)(1) The sex-linked recessive lethal test in *Drosophila melanogaster* shall be conducted with ODA in accordance with § 798.5275 of this chapter except the provisions of paragraph (d)(5)(iii), should a positive result occur in the detection of gene mutations in somatic cells in culture conducted pursuant to paragraph (c)(3)(ii)(A) of this section.

(2) *Exposure route.* The route of exposure shall be oral.

(C)(1) The mouse visible specific locus test shall be conducted with ODA in accordance with § 798.5200 of this chapter except the provisions for paragraphs (d)(3)(i), (5)(ii), and (iii), should a positive result occur in the sex-linked recessive lethal test in *Drosophila melanogaster* conducted pursuant to paragraph (c)(3)(ii)(B) of this section, if required following a public program review.

(2) For purposes of this section, the following provisions also apply.

(i) *Animal selection.* The mouse shall be used as the test species.

(ii) *Dosing.* A minimum of two dose levels shall be tested.

(iii) *Exposure route.* The route of exposure shall be oral.

(iii) *Reporting requirements.* (A) Gene mutation tests shall be completed and final results submitted to the Agency as follows:

(1) The detection of gene mutations in somatic cells in culture within 8 months of the effective date of the final test rule.

(2) The sex-linked recessive lethal test in *Drosophila melanogaster* (if required) within 17 months of the effective date of the final test rule.

(3) The mouse visible specific locus test (if required) within 48 months of

EPA's notification of the test sponsor by certified letter or **Federal Register** notice that testing should be initiated.

(B) Interim progress reports shall be provided at 6-month intervals beginning 6 months after the effective date of the final test rule or notification that testing should be initiated.

(4) * * *

(ii) *Test standard.* (A)(1) An oncogenicity bioassay, if required following a public program review, shall

be conducted with ODA in accordance with § 798.3300 of this chapter except the provisions of paragraphs (b)(1)(i) and (6)(i).

(2) For purposes of this section, the following provisions also apply.

(i) *Animal selection.* ODA shall be tested in both rats and mice.

(ii) *Exposure route.* The route of exposure shall be oral.

(iii) *Reporting requirements.* (A) The oncogenicity tests shall be completed

and final results submitted to the Agency within 53 months of EPA's notification of the test sponsor by certified letter or **Federal Register** notice that testing should be initiated.

(B) Interim progress reports shall be provided at 6-months intervals beginning 6 months after the submission of the study for this test.

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